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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

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Appellant(s): David H. Gelfand et al

Stacey R. Sias
For Appellant

EXAMINER'S ANSWER

Mailed
3-16-94

This is in response to appellant's brief on appeal filed Feb. 17, 1994.

(1) Status of claims.

The statement of the status of claims contained in the brief is correct.

While claims 40 and 41 have been indicated as allowable, these claims have been objected to as being dependent on a rejected claim.

(2) Status of Amendments After Final.

No amendment after final has been filed.

(3) Summary of invention.

The summary of invention contained in the brief is correct.

(4) Issues.

The appellant's statement of the issues in the brief is correct.

(5) Grouping of claims.

Appellant's brief includes a statement that claims 1, 35-39 and 53-62 do not stand or fall together and provides reasons as set forth in 37 C.F.R. § 1.192(c)(5) and (c)(6).

(6) Claims appealed.

The copy of the appealed claims contained in the Appendix to the brief is correct.

(7) Prior Art of record.

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

4,943,531	Goff et al	7/1990(5/6/85)
4,409,200	Feller et al	10/1983
4,379,839	Spiegelman	4/1983

Kaledin et al, Biokhimiya, vol. 45, No. 4, pp. 644-651, 1980.

Kaledin et al, Biokhimiya, Vol. 46, No. 9, pp. 1576-1584, 1981.

MBR Product Information Sheet, "DNA POLYMERASE", 6/8/87.

(8) New prior art.

No new prior art has been applied in this examiner's answer.

(9) Grounds of rejection.

The following ground(s) of rejection are applicable to the appealed claims.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1, 35-39 and 53-62 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to a buffer as required by claim 40. See M.P.E.P. §§ 706.03(n) and 706.03(z).

The specification discloses(page 79, lines 10-14) that the storage buffer consists of glycerol, KCl, Tris-Cl pH 8.0, ethylenediaminetetraacetic acid(EDTA), dithiothreitol(DTT), NP-40, Tween 20 and gelatin. NP-40 is an ethoxylated alkyl phenol and Tween-20 is a polyoxyethylated sorbitan monolaurate(page 25, lines 2-6), and these are non-ionic detergents. The buffer disclosed on page 79 is the only description of a specific

working embodiment of a buffer that can be used to produce a storage stable composition of a thermostable polymerase enzyme. It is well known in the art that the activity of enzymes can vary substantially according to the environment in which the enzymes and that it is unpredictable as to activity that will be obtained in a new environment such as provided by a different buffer. For example, see page 49, lines 12-16, of the specification where there is substantial variation in activity of polymerase depending on the pH. Further, see lines 17-23, on page 49 how the activity of polymerase can vary according to the presence of nucleotide triphosphates and may not be consistent with an expected value. Also, see the remarks concerning Wu et al in the paragraph bridging pages 21 and 22 of this examiner's answer. Due to the highly sensitive nature of polymerase to its environment and unpredictability of how it may behave in different environments, it would be unpredictable as to buffers substantially different from that disclosed on page 79 that would provide the desired polymerase stability. The gelatin in the buffer disclosed on page 79 could be important to acceptable stability since Kaledin et al(1980) disclose(page 497, 5th paragraph) that gelatin stabilizes DNA polymerase. Further see page 1250 of Kaledin et al(1981) as to the stabilizing affect of gelatin. The present claims encompass buffers substantially different from the buffer disclosed on page 79. Just any buffer components in combination with any non-ionic polymeric detergent

would not be expected to effectively stabilize the claimed polymerase based merely on obtaining effective stabilization with the specific buffer components in combination with a specific combination of non-ionic polymeric detergents as disclosed on page 79. Selecting other workable combinations that provide acceptable stabilization would require undue experimentation.

REJECTION UNDER 35 U.S.C. § 102

Claims 1, 35-39 and 53-59 are rejected under 35 U.S.C. § 102(a) as being anticipated by the MBR Product Information Sheet(hereafter referred to as MBR).

The present claims are drawn to a stable enzyme composition comprising a purified thermostable nucleic acid polymerase enzyme in a buffer containing one or more non-ionic polymeric detergents.

MBR discloses a shipping and storage buffer for DNA polymerase from Thermus aquaticus. This is the same enzyme as may be required by the present claims. See claims 57 and 58. The shipping and storage buffer contains Tris-HCl pH 7.5, KCl, EDTA, dithiothreitol, Tween-20 and glycerol. The present claims encompass a buffer containing DNA polymerase as disclosed by MBR. MBR was first circulated on June 8, 1987(paragraph bridging pages 6 and 7 of the Information Disclosure Statement of Aug. 3, 1992(paper no. 22)). This date is before the filing date of June 17, 1987 of parent application Serial No. 06/063,509 which is the first parent application disclosing the presently claimed

invention(see the above noted paragraph and page 10, lines 22-25, of the brief).

REJECTIONS UNDER 35 U.S.C. § 103

Claims 60-62 are rejected under 35 U.S.C. § 103 as being unpatentable over MBR.

It would have been a matter of obvious choice to obtain the DNA polymerase of MBR from other microorganisms known to produce the polymerase as in claims 60 and 61. Using the polymerase composition of MBR in a reaction mixture as required by claim 62 would have been obvious since DNA polymerase is normally reacted in such a mixture.

Claims 1, 35-39, 53-59 and 62 are rejected under 35 U.S.C. § 103 as being unpatentable over Kaledin et al(1980) in view of Goff et al, and if necessary in further view of Feller et al or Spiegelman.

The invention has been described in the rejection above.

Kaledin et al(1980) disclose isolating DNA polymerase from a thermophilic Thermus aquaticus. For example, see page 496, under "RESULTS AND DISCUSSION". The polymerase is stabilized by gelatin(page 497, 5th paragraph).

Goff et al disclose(col 8, lines 16-25 and col 20, lines 24-26) extracting DNA polymerase from cells and that loss of activity is prevented by the presence of a non-ionic detergent. A storage buffer containing the non-ionic detergent, NP-40, is disclosed at col 13, lines 62-64).

Feller et al disclose(col 7, lines 5-15 and col 15, lines 28-35) using a buffer containing the non-ionic detergent, NP-40, when equilibrating, washing and eluting in a procedure for using a chromatographic column to purify reverse transcriptase which is a DNA polymerase(paragraph bridging cols 1 and 2).

Spiegelman discloses(col 6, lines 26-27) using a buffer containing the non-ionic detergent, Triton X-100, for equilibrating and eluting when gel filtration for purifying DNA polymerase(reverse transcriptase).

It would have been obvious to store the DNA polymerase of Kaledin et al(1980) in a buffer containing a non-ionic polymeric detergent in view of Goff et al teaching that the presence of a non-ionic detergent prevents the loss of DNA polymerase activity during the purification of the DNA polymerase and disclosing a storage buffer containing a non-ionic detergent. To use a non-ionic detergent for its expected function to prevent activity loss as taught by Goff et al in a buffer during storage of the DNA polymerase of Kaledin et al(1980) would have been within the ordinary skill of the art and not unobvious. Combining a non-ionic detergent with the gelatin used by Kaledin et al(1980) would have been expected to provide better stability than gelatin alone. The use together of two known materials for preventing activity loss to obtain their functions in combination would have been obvious. If needed, further suggestion for the presence of a non-ionic detergent in a storage buffer for DNA polymerase

would have been provided by Feller et al or Spiegelman disclosing a non-ionic detergent in buffers used in the purification of DNA polymerase. In regard to claim 62, it would have been obvious to add the buffer containing DNA polymerase and non-ionic detergent to a known reaction mixture for which DNA polymerase is known to be added for carrying out a reaction. The limitations of the dependent claims would have been matters of obvious choice in view of the disclosures of the references.

Claims 60 and 61 are rejected under 35 U.S.C. § 103 as being unpatentable over the references as applied to claims 1, 35-39, 53-59 and 62 above, and further in view of Kaledin et al(1981) or Ruttimann et al(1985).

The present claims require obtaining DNA polymerase from Thermus flavus or Thermus thermophilus.

Kaledin et al(1981) disclose obtaining DNA polymerase from thermophilic Thermus flavus(see summary on page 1247).

Ruttimann et al disclose obtaining DNA polymerase from thermophilic Thermus thermophilus(see summary on page 41).

It would have been a matter of obvious choice depending on individual preference and convenience to substitute the DNA polymerase of Kaledin et al(1981) or Ruttimann et al for the DNA polymerase of Kaledin et al(1980).

(10) New ground of rejection.

This Examiner's Answer does not contain any new ground of rejection.

(11) Response to argument.

ARGUMENTS TO REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Beginning on page 9 of the brief, appellants urge that the examiner must present evidence or reasons to support why the specification is not enabling, and then the burden shifts to the applicants to show that one of ordinary skill in the art could have practiced the claimed invention without undue experimentation. This argument is unpersuasive since in the present case it is believed that reasons have been given sufficient to shift the burden to applicants.

Appellants on pages 10 and 11 of the brief refer to portions of the specification that disclose the invention as broadly as claimed. However, this is a general description based on speculation. It is incredible that any non-ionic detergent in combination with any other components to form a buffer could effectively stabilize DNA polymerase.

Appellants state that example XV on page 80 describes an experiment where the non-ionic detergent is omitted and this results in an inactive enzyme. However, the buffer from which the detergent was omitted is that formulated in the previous example XIV. This buffer is disclosed on page 79, lines 10-14. Additionally, in example XV, activity resulted when the non-ionic detergent was a mixture of the non-ionic detergents, NP-40 and Tween 20. There is inadequate support that this same activity would be obtained with any other non-ionic detergent alone or any

combination of non-ionic detergents when mixed with any other buffer components. The claims are clearly not commensurate in scope with examples XIV and XV.

In regard to claim 62, appellants urge that page 25 discloses the mixture of this claim with respect to carrying out an amplification process and that example XIV on page 62 specifically discloses this embodiment. However, in the reaction carried out in example XIV, the DNA polymerase used is that stored in the storage buffer disclosed on page 79, lines 10-14. Beginning at line 15, it is disclosed that the stored polymerase is diluted in a buffer. This buffer is similar to the storage buffer in containing both the non-ionic detergents, NP-40 and Tween-20, and further containing gelatin. The reaction buffer described by appellants on page 12 of the brief does not contain any non-ionic detergent.

In regard to appellants' argument in section 2 beginning on page 12 of the brief, it is believed that a reasonable explanation has been given as to why the scope of the claimed invention is not enabled by the description of the invention in the specification.

In section B beginning on page 14 and in section 2 beginning on page 20 of the brief, appellants urge that utility of the invention is being questioned. However, no rejection has been made under 101 and the rejection states that the disclosure is enabling only for claims limited to------, i. e. the claims are

not commensurate in scope with the invention enabled by the specification. Any question of utility is only that which is inherent in the rejection under 35 U.S.C. § 112, first paragraph.

It is granted that the specification goes into great detail. However, this detail is only with respect to a single embodiment and the claims encompass embodiments differing substantially from this embodiment. The single detailed embodiment is clearly not enabling for the many other embodiments within the scope of the claims. The specification fails to support that elements in the storage buffer on page 79 of the specification are non-critical as urged in this section and in the paragraph bridging pages 17 and 18 of the brief. If a single detergent or combinations of detergents other than exemplified can be used, then representative number of detailed working examples should have been provided using a single detergent and other combinations of detergents. Showing obtaining improved activity with only a combination of NP-40 and Tween-20 as the detergents is clearly not enabling for any single non-ionic detergent or any combination of non-ionic detergents as encompassed by the claims. If glycerol, Tris-HCl pH 8.0, ethylenediaminetetraacetic acid, dithiothreitol and gelatin are not critical and can be omitted, then a representative number of detailed working examples should have been presented showing results when these components are omitted.

Contrary to appellants' argument, the present invention is

not a simple invention since the invention involves stabilizing an enzyme that is made of a complex protein structure which may not be completely known. The protein structure can be easily denatured by conditions that break bonds that hold the structure together and result in uncoiling or unraveling of the structure. It is further pointed out that different non-ionic detergents can differ substantially in structure and chemical and physical properties. Such different non-ionic detergents would not be expected to affect the activity of an enzyme the same. Because of this unpredictability, it would be uncertain as to combinations of elements substantially different than used in the working examples in the specification that would provide acceptable DNA polymerase activity.

It is granted as urged by appellants in section 1 beginning on page 15 of the brief that a single example can be enabling. However, the claims must be commensurate in scope with this single example. In the present case, the claims are not commensurate in scope with the single embodiment described in detail. Broad and general description in the specification cannot substitute for working examples when there is unpredictability as in the present case.

Appellants refer to a Rule 131 Declaration filed 1/15/93(actually filed 1/19/93 as paper no. 26) as showing on page 57 of notebook no. 2610 that a problem of diminished activity was solved by adding non-ionic detergents to the enzyme

buffer. However, page 57 shows only the use of a combination of NP-40 and Tween-20 non-ionic detergents as providing improved activity. Also, the storage buffer contained KCl, Tris, DTT, EDTA and glycerol.

Appellants also refer to a Rule 132 Declaration(filed with preliminary amendment of 4/24/92) as demonstrating that when only the non-ionic detergent is omitted, the polymerase enzyme upon storage loses activity. However, this declaration was commented on in the paragraph bridging pages 5 and 6 of the office action of 7/15/92(paper no. 21). Also see the comments below concerning this declaration. It is not seen how the showing in experiment 1 that the presence or absence of NP-40 has no affect on functionality supports the breadth of the claims. It is known in the prior art that the enzyme does not require a detergent to function. The non-ionic detergent is being used in the invention to improve stability of the enzyme in a storage buffer and not to make the enzyme function. This experiment and experiments 2 and 3 do not store the enzyme in the buffer and then determine activity after a certain period of storage. In experiments 2 and 3, the non-ionic detergent that results in functionality is a combination of NP-40 and Tween-20 in combination with other specific components, and this composition is not required by the present claims. Experiment 3 is asserted to show that the replacement of NP-40 and Tween-20 with gelatin results in loss of functionality of the enzyme. However, this contradicts with the

Kaledin et al references which clearly disclose that DNA polymerase can function when gelatin is used as a stabilizer. See Kaledin et al(1980, page 497) where gelatin is used to stabilize DNA polymerase activity and this stabilized DNA polymerase is capable of its known function. This experiment fails to show results obtained when gelatin is present in combination with the non-ionic detergents as in example XIV in the specification. Since the example uses this combination, apparently the combination was found to provide better results. It is further noted that in experiment 1, the enzyme is reverse transcriptase whereas in experiments 2 and 3 the enzyme is DNA polymerase. It is uncertain as to whether these are intended to be different enzymes or the same enzyme. The source of the reverse transcriptase in experiment 1 is not given.

ARGUMENTS TO THE REJECTION UNDER 35 U.S.C. § 102

Beginning on page 27 of the brief, appellants urge that the Declarations under 37 C.F.R. § 1.131 of 4/24/92(attached to preliminary amendment of same date) and 1/19/93 establishes priority of the present invention. Appellants further urge that the disclosure of MBR was derived from applicants.

However, the 37 C.F.R. § 1.131 Declarations establish priority for only a specific species that is not required by the present claims, and not priority for the claimed generic invention. MPEP 715.03 states that in chemical cases the declaration must show possession of the generic invention prior

to the date of the reference. The species disclosed by MBR is different from the species enabled in the present specification. The Declaration of 4/24/92 was responded to in the office action of 7/15/92(paper no. 21). The evidence in the declaration is a letter to MBR containing an attachment disclosing a purification protocol for DNA polymerase from Thermus aquaticus. See the attachment to the 131 declaration of 2/11/91 in parent application Serial No. 07/387,003 that was defective in not being signed by all the inventors. This letter is further presented as part of exhibit B attached to the brief. The 2X storage buffer disclosed on the last page of the attachment(line 4 from the last line) contains Tris-Cl pH 8, KCl, EDTA, DTT, glycerol, NP-40 and Tween-20, and the polymerase is DNA polymerase from Thermus aquaticus. It should be noted that DTT is dithiothreitol and EDTA is ethylenediaminetetraacetic acid. The present claims do not require this species. The buffer of MBR is different in that it contains only Tween-20 as a non-ionic detergent. The composition of the invention formulated prior to MBR as shown by the declaration contains both NP-40 and Tween-20, and not just Tween-20 as found by MBR to be adequate. The buffer of MBR further does not contain gelatin which the present specification indicates is required. See example XIV where the composition contains gelatin. The declaration establishes priority for only one species that is different from the species of MBR and this one species is not required by the present claims. The 131

declaration does not establish priority of the claimed generic invention of using any buffer components in combination with any non-ionic detergent or any combination of such detergents. The Declaration of 1/19/93 like the Declaration of 4/24/92 establishes only priority for a specific species as set forth above. In all experiments shown by the exhibits according to the invention, both NP-40 and Tween-20 are present. This declaration has been commented on in the office action of 3/19/93 in the paragraph bridging pages 4 and 5.

Appellants urge that decisions support that a 131 Declaration is sufficient if it shows prior possession of the invention disclosed by the reference. However, as noted above, the 131 declarations do not show possession of the composition of MBR that contains only Tween-20, but show possession of a different composition containing both NP-40 and Tween-20. Additionally, the composition enabled in the specification contains gelatin and the MBR composition does not contain gelatin. The 131 Declarations do not show prior possession of the claimed generic invention.

As to appellants' argument that MBR derived the disclosed composition from appellants, this does not appear to be the case since, as noted above, the composition disclosed by MBR is different from the composition shown possession of in the 131 Declarations and enabled in the present specification. Moreover, the 35 U.S.C. § 103 rejection over Kaledin et al(1980) in view of

Goff et al, and if necessary in further view of Feller et al or Spiegelman supports that MBR could have derived the composition from information provided by the references independent of information obtained from appellants.

ARGUMENTS TO REJECTIONS UNDER 35 U.S.C. § 103

Appellants assert that MBR has been overcome by the 131 Declarations. However, the declarations fail to antedate MBR in regard to the 103 rejection for the same reasons as set forth above in regard to the 102 rejection. Appellants have established no unexpected result in obtaining DNA polymerase from Thermus flavus or Thermus thermophilus as compared to the aquaticus species. It is known that the flavus and thermophilus species produce DNA polymerase and it would have been a matter of obvious choice to obtain the enzyme from these sources. Appellants have not asserted that they are the first to obtain DNA polymerase from these sources.

The arguments concerning the references beginning on page 44 of the brief are directed to the references individually. However, the rejection is based on the references in combination and not each alone. While Kaledin et al(1980) uses gelatin for stabilizing DNA polymerase, it would have been apparent from the Goff et al and if needed Feller et al or Spiegelman that the presence of a non-ionic detergent is beneficial in maintaining activity of the enzyme during purification. This disclosure would have suggested that a non-ionic detergent will help

maintain the activity of DNA polymerase in a storage buffer and it would been obvious for this reason to combine a non-ionic detergent with the gelatin used by Kaledin et al to obtain improved activity during storage. Even in the absence of gelatin, it would have been expected that the detergent would provide improved activity in a storage buffer as compared to when not being present in view of the affect of the detergent on activity during purification as disclosed by Goff et al and the use of the detergent in purification as disclosed by Feller et al or Spiegelman.

In the first paragraph on page 46 of the brief, appellants assert that the specification(apparently this is in reference to the specification of Goff et al) is silent on and does not require the a non-ionic detergent in elution buffers. However, Goff et al disclose(col 20, lines 24-26) that the presence of a non-ionic detergent is required throughout the purification to prevent aggregation and loss of activity. If the detergent is required to maintain activity during purification, it would have been expected that the detergent would be beneficial for activity during storage. Further see col 13, lines 56-64, where the buffers used including a storage buffer contain the non-ionic detergent, NP-40. The desire to maintain activity would have been motivation to store DNA polymerase in the presence of a non-ionic detergent. While the DNA polymerase of Goff et al is not disclosed to be thermostable, there us seen nothing in being

thermostable that would have led one to believe a non-ionic detergent would not maintain activity as suggested by Goff et al. A thermostable DNA polymerase is still a DNA polymerase. It is granted that the DNA polymerase of Goff et al is produced by genetic engineering techniques. However, Feller et al and Spiegelman disclose using buffers containing a non-ionic detergent when purifying non-genetically engineered DNA polymerase. Thus, when the references are considered in combination, it is apparent that the presence of a non-ionic detergent helps maintain activity of DNA polymerase irrespective of whether it is produced by genetic engineering or obtained from a microorganism in which it occurs as disclosed by Kaledin et al.

Kaledin et al(1981) is not relied to disclose the use of non-ionic detergents but to disclose specific microorganisms from which DNA polymerase can be obtained. However, like Kaledin et al(1980) this reference discloses that gelatin stabilizes DNA polymerase.

Appellants assert that the 132 Akers Declaration(exhibit D) shows that reverse transcriptase functions equivalently in the absence or presence of the non-ionic detergent, NP-40. However, as stated above, it is known that the detergent is not needed for the enzyme to function. The DNA polymerase of Kaledin et al(1980 and 1981) can function in the absence of a detergent. The detergent is used by Goff et al, Feller et al and Spiegelman to maintain activity during purification and not to cause the enzyme

to function in a process of use. Furthermore, the present claims are not directed to a process where the enzyme functions but to a composition for storage of the enzyme. The enzyme is not functioning in the composition since it is not being used in a process. Additionally, the declaration fails to disclose the source of the reverse transcriptase and how it differs from the DNA polymerase in experiments 2 and 3. In the art, reverse transcriptase can be a DNA polymerase. See Feller et al(paragraph bridging cols 1 and 2), Goff et al(col 8, lines 16-18) and Spiegelman(col 2, line 4). In experiments 2 and 3, functionality was obtain with a combination of NP-40 and Tween-20 in combination with other specific buffer components and this composition is not required by the present claims. Moreover, obtaining no functionality in the absence of the detergents and when gelatin is present in these experiments is inconsistent with Kaledin et al(1980 and 1981) where the same DNA polymerase as used in the experiments is capable of functioning in the absence of a detergent and the enzyme is stabilized with gelatin. If the reverse transcriptase in experiment 1 has DNA polymerase activity, the results of experiments 2 and 3 are also inconsistent with the result of experiment 1 where functionality is obtained in the absence of a detergent. In view of the present specification(paragraph bridging pages 24 and 25), the purpose of the detergent is to provide the DNA polymerase with long-term stability during storage. There is no disclosure in

the specification of the detergent being needed for the polymerase to function in a process when the polymerase is not stored. Experiments 1, 2 and 3 do not show storing the DNA polymerase in the buffers tested for different periods of time and then determining activity. Moreover, such experiments should include a showing of results from combining gelatin with NP-40 and Tween-20 since this combination is disclosed in the working examples in the specification.

The 132 Gelfand Declaration(Exhibit E) sets forth conclusions without adequately describing experiments or procedures carried out that led to the conclusions. While a difference in amino acid sequence is asserted, how this difference was determined has not been specifically described. Additionally, how the amino acid sequences differ has not been specifically set forth. Furthermore, there is nothing to establish that a difference in amino acid sequence affects how the enzyme will behave in the presence of a detergent. Feller et al and Spiegelman disclose using a non-ionic detergent in purifying DNA polymerase different than disclosed by Goff et al and this suggests that a non-ionic detergent maintaining the activity of DNA polymerase is not limited to a specific type of DNA polymerase.

Appellants urge that Wu et al(Exhibit F) found non-ionic detergent stimulation of viral reverse transcriptase(DNA polymerase)(line 2 of abstract) but did not observe this effect

with bacterial DNA polymerase. However, when determining whether bacterial DNA polymerase is stimulated, it appears that only Triton X-100 is used as the detergent(see Table III, page 791). Additionally, in carrying out all the tests of detergent stimulation, only a single detergent is used each time. The Triton X-100 detergent or other detergents used alone may not have had any affect on the DNA polymerase of the claims. As set forth above, the specification and the 131 and 132 Declarations show obtaining a stabilizing affect only when a combination of NP-40 and Tween-20 are used, and the specification enables only a composition which also contains gelatin. Furthermore, Wu et al provides support for the 112 breadth rejection since this reference indicates unpredictability and that certain detergents within the scope of the claims will not stabilize bacterial DNA polymerase. While Wu et al disclose that stimulation is dependent on the amount and type of template-primer, in Table I it appears that stimulation is obtained without the presence of template-primer. It should be noted that in Table I viral DNA polymerase and not bacterial DNA polymerase is being tested for stimulation by the different detergents.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

DMN
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